RADIATION RESEARCH **138,** 326–336 (1994)

Exposure to Radon Progeny, Tobacco Use and Lung Cancer in a Case-Control Study in Southern China

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Yao, S. X., Lubin, J. H., Qiao, Y. L., Boice, J. D., Jr., Li, J. Y., Cai, S. K., Zhang, F. M. and Blot, W. J. Exposure to Radon Progeny, Tobacco Use and Lung Cancer in a Case-Control Study in Southern China. *Radiat. Res.* 138, 326–336 (1994).

A case-control study of lung cancer in underground tin miners in southern China was conducted to examine the interplay between exposure to radon progeny and tobacco use. A total of 460 incident cases and 1,043 controls were evaluated. Among the exposed, mean radon progeny exposures were 600 and 427 working level months (WLM) for cases and controls, respectively. The excess relative risk per WLM (ERR/WLM) was 0.28% overall, with a 95% confidence interval of 0.1–0.6%, similar to the estimate from a cohort study in a related population of underground miners. The established patterns of lung cancer associated with radon were seen; the ERR/WLM decreased with attained age and time since last exposure. Conditional on total exposure, risk was highest for exposures delivered at a low rate. The ERR/WLM did not differ significantly among current and former smokers or within categories of time since last exposure. The relative risk relationship between exposure to radon progeny and tobacco use was consistent with a multiplicative model, but the best-fitting model was intermediate between additive and multiplicative; an additive association was rejected. Adjustment for exposure to inorganic arsenic, a known lung carcinogen, reduced the estimate of the ERR/WLM from 0.86% to 0.28%. The ERR/WLM estimate was homogeneous across subgroups defined by workers not exposed to arsenic and quartiles of cumulative arsenic exposure. Although squamous cell carcinoma was the predominant cell type, small cell and adenocarcinoma histologies appeared more strongly associated with exposure to radon progeny. The finding of a stronger trend with exposure with small cell carcinomas and adenocarcinomas, compared to squamous cell carcinomas, occurred primarily at younger ages at diagnosis. Finally, the risk of lung cancer was higher if exposure to radon progeny and tobacco use occurred together than if the exposure to radon progeny entirely preceded tobacco use.

INTRODUCTION

Among underground miners, exposure to elevated levels of radon (or more precisely ^{222}Rn) and its progeny can cause lung cancer *(1–3).* While the carcinogenicity of exposure to radon progeny is clear, there is a substantial gap in our understanding of: (1) the role of tobacco use in the risk of lung cancer from exposure to radon progeny, as few studies with detailed information on tobacco use have been carried out; and (2) the relationship between exposure to radon progeny and histological type. A case-control study of lung cancer among radon-exposed tin miners in southern China was conducted to examine the interplay between radon exposure and tobacco use and radon exposure and histological type. A total of 460 cases and 1,043 controls were evaluated.

There have been two studies which included information on both tobacco use and exposure to radon progeny and which also had large numbers of cases, the Colorado Plateau uranium miners study with 256 lung cancer cases *(4, 5),* and the Chinese tin miners study, with 907 cases with tobacco use information (out of a total of 980 lung cancer cases) *(6).* There have been several other studies with data on tobacco use *(7–9),* but due to limited numbers of cases these studies generally lacked the power to discriminate among the various models for the joint association *(1).*

The Colorado study and the China study were both cohort studies. Information on tobacco use came principally from medical records or from intermittent surveys and may

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0033-7587/94 $5.00

not have adequately reflected smoking practices, particularly after employment ceased. For example, in the China study, data on tobacco use were obtained from a single occupational survey conducted in 1976. The smoking data were missing on 24% of the subjects (including 73 lung cancer cases) and were limited, so that only the dichotomy, never-smoker or smoker, could be analyzed. In the Colorado study with follow-up through 1987, data on tobacco use were available only as late as 1969, with no subsequent information. In addition, in neither of these analyses were the effects of cessation of radon exposure or cessation of smoking considered.

As a companion to the Chinese cohort study *(6)*, which involved 17,000 workers of the Yunnan Tin Corporation (YTC) in southern China, we conducted a case-control interview study of all incident lung cancers among males who worked at the YTC or resided in Gejiu City, where the YTC is located. Extensive information on tobacco use, as well as other information, was obtained from the direct interview of subjects or their next-of-kin. The effects of diet and smoking practices on the risk of lung cancer in these populations have been reported *(10, 11)*. In addition, skeletal ^{210}Pb activity has been evaluated as a direct indicator of exposure to radon progeny *(12)*.

METHODS

Gejiu City has approximately 370,000 people and is located in the southern part of Yunnan Province. The largest employer in the area is the YTC with about 52,000 active and retired workers. The YTC operates 5 underground mines, 9 ore dressing plants, 3 smelters and 11 other related factories. The YTC maintains contact with retired employees through payment of retirement benefits and company-provided medical care, and few workers leave the company prior to retirement; ascertainment of cancer among YTC workers is therefore thought to be complete. About 80–100 cases of lung cancer are reported annually to the YTC Registry.

The Gejiu City municipal government also owns and operates several small underground tin mines, as well as maintains a population-based Cancer Registry. which annually records about 20–30 additional lung cancer cases in males.

For our case-control study, we sought to enroll all cases of lung cancer among males, aged 35–75, who were reported to the Cancer Registry at the Labor Protection Institute of the YTC or to the Gejiu City Cancer Registry between 1984 and 1988. To ensure uniform case definition, an independent panel of pathologists, clinicians, radiologists and cytologists reviewed the diagnoses of all lung cancer cases.

For each Gejiu City lung cancer case, two controls were selected randomly from the general population of city residents, and for each YTC case we randomly selected one control from the YTC population and one control from the joint population of Gejiu City and the YTC. Controls were matched on age within 5 years of its case.

Interviews were conducted in the subject's home, in a city or company hospital or at the work site by a trained interviewer, using a standardized, structured questionnaire. Next-of-kin, usually the spouse, were interviewed for subjects who were deceased or who were not available after three visits by an interviewer. The subjects interviewed represent 92% and 91% of cases and controls who were identified initially, respectively; the remainder could not be located or had moved to a distant area and were not interviewed.

For each underground YTC worker, exposure in units of working level months[2] (WLM) was estimated from work history records and measurement data of WL levels. After 1972, WL data from over 26,000 area measurements were available. Industrial hygienists with assistance from older workers adjusted values to reflect unmeasured work areas and job title. For 1953–1972, estimates of WL were based on 413 recent measurements which were obtained by recreating conditions in tunnels and galleries in original areas or by measuring similarly configured areas in nearby non-YTC mines which operate using techniques similar to those in the index years. Prior to 1953, estimates of WL were based on 117 recent measurements taken by recreating primitive mine conditions in 13 local small mine pits that were in operation before 1949 *(13)*. For municipal miners, estimates of WLM were based on the available historical data from YTC and non-YTC mines in proximity and on WL measurements which were collected on a regular basis starting in 1976.

Subjects who worked underground were potentially exposed to inorganic arsenic in mine dusts as well as to radon and its progeny. Arsenic exposure was estimated using data on airborne dust concentrations, which have been measured extensively since the 1950s. A cumulative exposure index for arsenic exposure was computed as mg-months/m^3.

Tobacco was consumed mainly in the form of cigarettes, water pipes and Chinese long-stem pipes. For the analyses in this report, amounts of tobacco in *liang* (50 g) used in water and long-stem pipes were combined, while duration of use was the maximum of years of use of water pipe or long-stem pipe. For pipe users, cessation of pipe use was defined as the minimum time since cessation of the use of water pipe or long-stem pipe. Further details of the case-control study design and other characteristics of the population have been published *(6, 10)*.

Previous analyses indicated that the relative risk (RR) of lung cancer increases approximately linearly with cumulative WLM. Stratification and adjustment variables were modeled as multiplicative factors. For a vector of controlling factors x, the odds of lung cancer outcome were specified as $\exp(\alpha x) \times \mathrm{RR}$, with the following model for (continuous) WLM exposure:

$$\mathrm{RR} = 1 + \beta \times \mathrm{WLM} \tag{1}$$

where β was the exposure–response parameter in units of excess RR per WLM (ERR/WLM). The modification of the ERR/WLM by categories of other factors, such as age, time since last radon exposure and exposure rate in WLM/year, was considered by comparing the deviance of model (1) with the deviance of a model in which β varies by categories of another factor. For example, if factor z consists of J levels, with values $z_1, \ldots z_J$, then model (1) was compared with model (2),

$$\mathrm{RR} = 1 + \beta_j \times \mathrm{WLM}, \tag{2}$$

where β_j is the ERR/WLM within level j. Under the null hypothesis that the ERR/WLM is the same for all levels, the difference in the deviances is approximately χ^2 with $J - 1$ degrees of freedom.

Initial analyses suggested that individual matching of controls to cases was unnecessary. Matching was therefore dropped, with matching factors included as covariates or as stratification variables in the risk regression models. All analyses stratified on source of subject (YTC or Gejiu City), type of respondent (subject or next-of-kin) and age group (defined by quartiles, <57, 58–62, 63–67, >=68 years). In addition, all analyses were adjusted for arsenic exposure (defined by no arsenic exposure and quartiles of mg-months/m^3).

[2]One working level (WL) equals any combination of radon progeny in one liter of air which results in the ultimate emission of 130,000 MeV of energy from α particles. WLM is a time-integrated exposure measurement and is the product of time, in units of working months which is taken to be 170 h, and working levels.

TABLE I

Relative Risks (RR) of Lung Cancer among Chinese Tin Miners by Category of Exposure to Radon Progeny

	Exposure to radon progeny (WLM)					
	0	1–199	200–399	400–799	>=800	Total
Cases	79	48	72	159	102	460
Controls	470	171	146	174	77	1038
Mean WLM	0.0	102.0	305.7	557.5	1067.2	314.4[a]
RR[b]	1.00	1.85	3.37	6.49	9.50	
95% CI		(1.2–2.9)	(2.2–5.2)	(4.4–9.6)	(6.0–14.9)	
RR[c]	1.00	0.71	1.15	1.82	2.43	
95% CI		(0.3–1.7)	(0.5–2.7)	(0.8–4.3)	(1.0–5.9)	

[a] Among exposed, mean WLM was 496.6, with 599.9 for cases and 427.3 for controls.

$$RR = \theta^{f}(1 + \beta \times WLM),$$

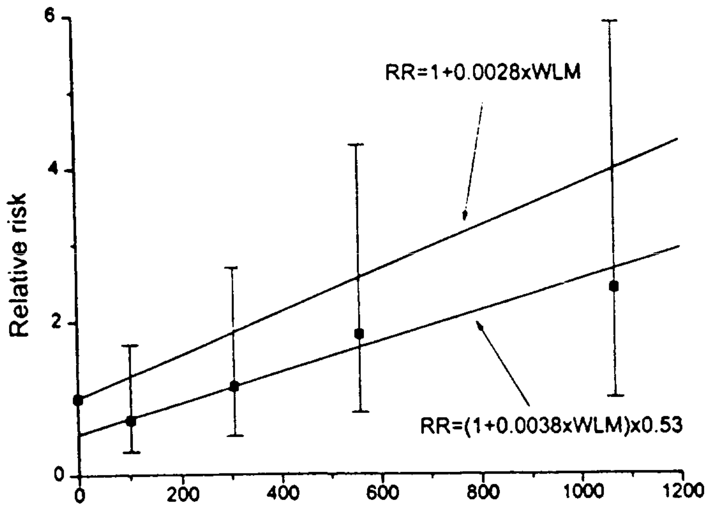

TABLE II
Relative Risks (RR) of Lung Cancer among Chinese Tin Miners by Method of Tobacco Use

Method of consumption	Cases	Controls	RR[a]	95% cl
Never-smoker	9	74	1.00	
Cigarettes only	55	197	3.36	(1.3–8.3)
Pipes only	57	153	1.68	(0.7–4.1)
Mixed	339	619	4.19	(1.8–9.7)
Total	460	1043		

[a] RRs adjusted for age, source of subject (Gejiu City or YTC) and type of respondent.

using both cigarettes and pipes. About 2% of cases and 7% of controls never smoked. Smokers were at 2- to 4-fold the risk of lung cancer compared to never-smokers.

The numbers of cases and controls in Table II differ from those in Table III in an earlier analysis by Lubin *et al.* *(10)* because of the handling of missing values. The earlier analysis focused on method of consumption, and subjects were therefore excluded if method-specific information was missing. In the current analysis, definitions of variables for mixed cigarette and pipe use were modified to minimize the exclusion of subjects. For example, for mixed smokers, duration of smoking was taken as the maximum number of years of cigarette use, water pipe use and long-stem pipe use. A missing value for one of these variables would have excluded the individual from the previous analysis, but not from the current analysis.

TABLE III
Excess Relative Risk of Lung Cancer per WLM[a] (ERR/WLM) and Its Variation with Several Factors

	Cases	Controls	(ERR/WLM)%	P^b
Overall	460	1038	0.28[c]	
Attained age (quartiles)				
<58	108	238	0.31	<0.001
58–62	125	258	0.44	
63–67	107	274	0.17	
≥68	120	268	0.15	
Years since last radon exposure[d]				
0	31	11	1.27	0.006
1–9	102	129	0.20	
10–19	57	72	0.21	
≥20	191	356	0.13	
Radon progeny exposure rate (WLM/year)[d]				
<15	57	103	0.58	0.03
15–24	124	155	0.53	
25–34	166	244	0.30	
≥35	34	66	0.16	
Age at first radon exposure[d]				
<10	35	28	0.38	0.58
10–14	167	185	0.30	
15–19	82	115	0.25	
20–24	38	73	0.18	
≥25	59	167	0.30	
Smoking status				
Never-smoker	9	74	0.51	0.61
Ever smoker	451	964	0.26	
Years since cessation of smoking[e]				
<5	414	850	0.29	0.67
≥5	34	111	0.20	

[a] All models were stratified by smoking status, age, source of subject (Gejiu City or YTC) and type of respondent (individual or surrogate).
[b] *P* value for test of homogeneity of ERR/WLM over categories of modifying variables.
[c] For overall ERR/WLM, 95% CI was 0.1–0.6%.
[d] Distribution of cases and controls among radon-exposed workers.
[e] Distribution of cases and controls among smokers.

TABLE IV
Relative Risks (RR) of Lung Cancer by WLM and Smoking Rate among Chinese Tin Miners

Smoking rate[a]	Exposure to radon progeny (WLM) 0	1–199	200–399	400–799	>=800	Total	RR[b]
0	0.53	0.52	0.39	0.82	7.61		0.83
	2/39	2/15	1/8	2/10	2/2	9/74	
I	1.00[c]	0.77	0.75	1.00	1.26		1.00[c]
	19/178	10/46	8/49	25/77	13/26	75/376	
II	1.60	0.67	1.47	3.63	2.54		2.00
	21/147	10/69	19/58	39/53	24/29	113/356	
III	5.69	5.42	8.59	12.4	13.2		9.00
	37/109	26/42	44/30	93/34	63/21	263/236	
RR[b]	1.00	0.69	1.05	1.78	1.80		
Total	79/473	48/172	72/145	159/174	102/78		

[a] Smoking rate equals the number of cigarettes per day plus twice the number of *liang* per month. Categories are defined by never-smokers (0), and values of 1–13 (I), 14–23 (II) and 24 and greater (III).
[b] RRs based on multiplicative model for WLM and smoking rate; all RRs were adjusted for study, type of respondent and attained age.
[c] Referent level for the RRs.

Cigarette smokers consumed approximately 13 cigarettes per day (15 cigarettes per day for smokers of cigarettes only and 13 cigarettes per day for mixed smokers), while pipe smokers consumed 5.3 *liang* per month (5.5 *liang* per month for pipe-only smokers and 5.3 *liung* per month for mixed smokers). Based on the results in Table II, the RR per cigarette per day is about half of the RR per *liang* per month. We combined cigarettes smoked per day and *liang* smoked per month to create a smoking rate variable equal to the number of cigarettes per day plus twice the *liang* smoked per month. The variable was then categorized into never-smokers and tertiles of the rate of tobacco use. For mixed cigarette and pipe smokers, years since stopping smoking was computed as the minimum time since last use of cigarettes or pipes.

ERR/WLM Modification Variables

Previous analyses of YTC miners and of pooled data from multiple cohorts of underground miners exposed to radon have shown that the ERR/WLM declined with increasing attained age, years since last radon exposure and increasing radon progeny exposure rate, while no significant variation was found with age at first exposure to radon progeny *(1, 2, 6)*. These same patterns were observed in the current data (Table III). Note that the variation of the ERR/WLM with exposure rate implies that conditional on total WLM, the RR of lung cancer was greater for those exposed for a long duration at low exposure rate compared with those exposed for a short duration at a high exposure rate.

Joint Effects of Exposure to Radon Progeny and Tobacco Use

Table III also shows that the ERR/WLM did not differ significantly by smoking status, indicating that the joint association between exposure to radon progeny and smoking is consistent with a multiplicative relationship. However, the ERR/WLM for never-smokers is larger in value, which suggests a sub-multiplicative relationship. Among smokers, the ERR/WLM did not differ significantly by categories of years since cessation of tobacco smoking.

The RRs and the joint distribution of WLM and smoking rate are shown in Table IV. The risk in the highest category of the smoking rate groups was almost 11-fold (9.0/0.83) compared to never-smokers, whereas an 80% increase was observed for those exposed to 800 WLM and more compared to those not exposed to radon progeny. The RR trends for WLM exposure are generally consistent, overall and within smoking categories.

Table V shows the overall ERR/WLM within each smoking rate category. While the largest ERR/WLM occurred in never-smokers, suggesting a sub-multiplicative relationship for the joint association, a multiplicative model could not be ruled out; the *P* value for the test of homogeneity of ERR/WLM across the smoking rate categories was 0.48. Table V also shows ERR/WLM for smoking rate within levels of attained age, years since last exposure to radon progeny and years since cessation of smoking; the ERR/WLM patterns were unaffected by these factors.

Although not shown, the joint association of duration of smoking and exposure to radon progeny was evaluated, paralleling the analyses shown in Tables IV and V. The ERR/WLM estimates were homogeneous within smoking duration categories (never-smokers and tertiles of duration of tobacco use). The ERR/WLM estimates within duration categories did not change when data were stratified on attained age, years since last exposure to radon progeny and exposure rate.

TABLE V

ERR/WLM[a] of Lung Cancer by Categories of Never-Smokers and Tertiles of Smoking Rate, Overall and within Levels of Several Variables

	(ERR/WLM)% by smoking rate[b]				
	0	I	II	III	P[c]
Overall	0.47	0.09	0.27	0.29	0.48
Attained age					
<63	0.58	0.10	0.26	0.33	0.94
≥63	0.40	0.08	0.26	0.12	0.80
Years since last radon exposure					
<10	0.26	0.03	0.30	0.32	0.29
≥10	0.54	0.12	0.26	0.14	0.25
Radon progeny exposure rate (WLM/year)					
<25	0.00	0.17	0.25	0.72	0.31
≥25	0.54	0.10	0.36	0.18	0.29
Years since stopping smoking					
<5		0.09	0.31	0.27	0.28
≥5		0.16	0.25	0.20	0.52

[a] Models include strata parameters for age, study and type of respondent and multiplicative adjustment parameters for smoking rate and cessation of smoking.
[b] Smoking rate categories defined in Table IV.
[c] P value for test of homogeneity of ERR/WLM for categories of smoking rate, overall or within levels of second factor.

For the joint association of exposure to radon progeny and smoking rate or smoking duration, we fitted the following geometric mixture model

$$RR = [RR_S \times (1 + \beta WLM)]^{\lambda}(RR_S + \beta WLM)^{1-\lambda}, \quad (4)$$

where RR_S denotes the RR for smoking (either smoking rate or duration) and λ is the mixing parameter. For λ, a value of one denotes a multiplicative model, and a value of zero denotes an additive model. Model (4) also includes models greater than multiplicative ($\lambda > 1$), between multiplicative and additive ($1 > \lambda > 0$) and less than additive ($\lambda < 0$). RR_S was modeled using categories or a continuous variable with a log-linear trend. For each of the four models that were fitted (smoking rate or duration, as a categorical or continuous variable), the multiplicative model was never rejected, while the additive model was always rejected. While the joint associations were consistent with a broad range of models from sub-multiplicative to super-multiplicative, the best estimates for models in smoking rate indicated a super-multiplicative association, while the best estimates for models in smoking duration suggested a model intermediate between multiplicative and additive.

Timing of Exposure to Radon Progeny and Tobacco Use

To evaluate further the relationship between exposure to radon progeny and smoking and lung cancer risk, we classified workers according to whether they were exposed to radon progeny during the time in which they used tobacco. The classification scheme is defined in Fig. 2. For example, tobacco use occurred entirely within the interval of exposure to radon progeny for 17 cases and 15 controls (category 5), while no subjects stopped tobacco use before their first exposure to radon (category 8). Table VI shows the risks relative to category 3, where exposure to radon progeny occurred entirely before any use of tobacco. The RRs were highest, 3- to 4-fold, for exposure categories 4–7, where smoking and radon exposure overlapped; these categories in turn exceed the RR for the tobacco-only category (category 1). The lowest risk occurred for those not exposed to radon progeny or tobacco smoke.

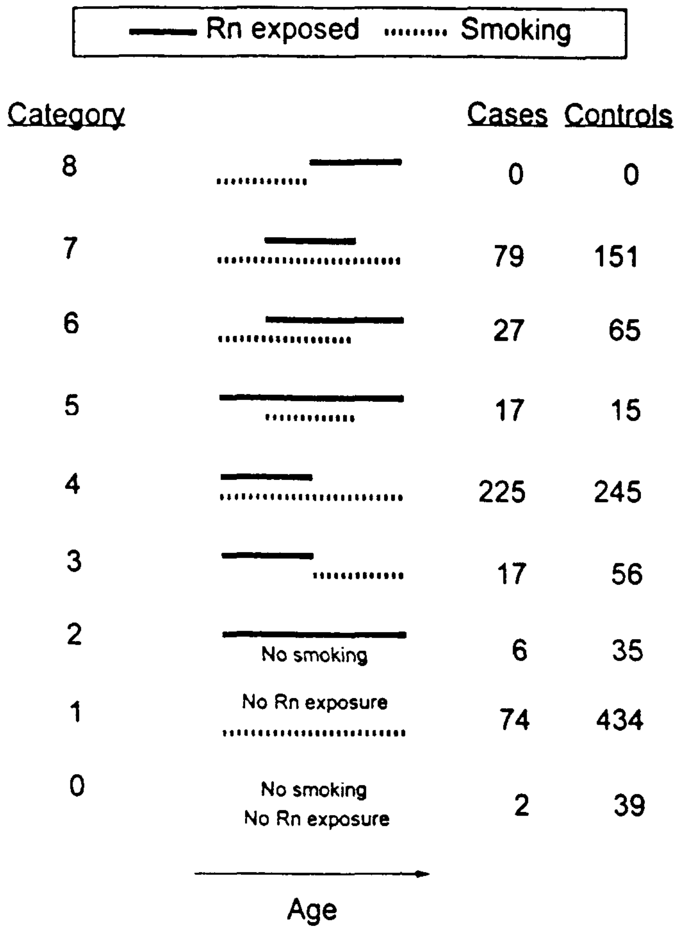

FIG. 2. Schematic representation of temporal exposure to radon (Rn) progeny and tobacco use.

Mean WLM and mean smoking rate varied by the temporal patterns shown in Fig. 2. To account for differences, we further stratified RRs for categories of WLM, smoking rate and years since cessation of smoking. Because of the further stratification, RRs for categories 0–2 are no longer estimable. The RRs for levels 4–7 were again similar and exceeded the referent category by 50 to 100%. To summa-

TABLE VI
Relative Risks (RR) of Lung Cancer by Various Temporal Patterns of Exposure to Radon progeny and Tobacco Smoking, as Defined in Figure 2

	Category of temporal pattern of exposure to radon progeny and tobacco smoking								
	0	1	2	3	4	5	6	7	Total
Cases	2	74	6	17	225	17	27	79	447
Controls	39	434	35	56	245	15	65	151	1,040
RR[a]	0.74	2.72	0.92	1.00[b]	3.45	3.16	3.23	4.60	
95% CI	(0.1–4.5)	(1.0–7.5)	(0.3–3.1)		(1.7–6.9)	(1.1–8.8)	(1.4–7.7)	(2.0–9.0)	
RR[c]				1.00[b]	1.82	1.53	1.63	2.06	
95% CI					(0.7–4.9)	(0.4–6.4)	(0.5–5.6)	(0.7–6.2)	

[a] RRs are stratified by study site, type of respondent and age group.
[b] Referent level for RRs.
[c] RRs among radon-exposed miners and smokers, with additional stratification by WLM, smoking rate and years since cessation of smoking. RRs for patterns 0–2 are not estimable with the additional stratification.

rize this difference, we defined an indicator variable taking value one for overlapping exposures (categories 4–7) and zero for nonoverlapping exposures (category 3). Adjusting for source of subject, type of respondent and age, the RR was 3.6 with 95% CI of 1.8–7.1; further stratification by WLM, smoking rate and cessation of smoking resulted in an RR of 1.8 with 95% CI of 0.7–4.9.

Histological Cell Type and Exposure to Radon Progeny

Histological cell type was determined for 407 of the 460 lung cancer cases (88%); the most common histological type was squamous cell carcinoma, which was likely due to the larger percentage of smokers. There were 279 squamous cell carcinomas (69%), 69 small cell carcinomas (17%), 46 adenocarcinomas (11%) and 11 other types (3%); two (squamous cell) cases had missing WLM data and are not considered further.

For each cell type, RRs were computed relative to all controls. For each cell type, RRs increased with increasing duration of smoking and smoking rate, with the risk compared to never-smokers greatest for squamous cell carcinomas. There were six lung cancer cases who never smoked; one was squamous cell carcinoma; one was small cell carcinoma and four were adenocarcinomas.

We estimated the ERR/WLM for each cell type using model (3). Results are shown in Fig. 3. For clarity, CIs are not shown, but were generally quite wide, particularly for small cell carcinomas and adenocarcinomas. The largest ERR/WLM estimate occurred for the adenocarcinoma cases and the smallest for the squamous cell cases. The estimates of the ERR/WLM and their 95% CI were 0.20% and 0.04–0.63% for squamous cell carcinomas, 0.54% and 0.07–6.07% for small cell carcinomas and 0.68% and 0.04%–17.9% for adenocarcinomas. These estimates did not differ significantly. Table VII shows the variation of the ERR/WLM estimates for each cell type by categories of several factors. The variations of the ERR/WLM appear generally consistent for the different cell types, although data are too limited for definitive conclusions.

Ignoring controls, we computed the odds ratios (OR) for categories of WLM for squamous cell relative to small cell carcinomas (denoted $OR_{SQ\text{-}SM}$) and for squamous cell carcinomas relative to adenocarcinomas (denoted $OR_{SQ\text{-}AD}$); the baseline category for WLM is zero exposure. Values of ORs greater than one indicate a positive association of WLM with squamous cell carcinomas compared to the referent tumor type, and values less than one indicate a positive association with the referent tumor type. Table VIII shows that ORs are generally greater than one. The *P* values for trend for squamous cell carcinomas relative to small

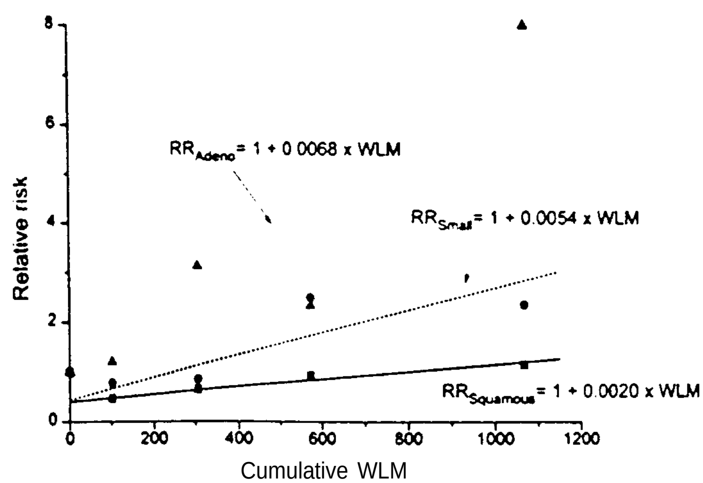

FIG. 3. Relative risks (RR) of lung cancer among Chinese tin miners and fitted linear excess RR models by histological cell type. Referent category for RRs is zero WLM. Models fitted with a free intercept (not shown). (■) Squamous cell carcinoma, (●) small cell carcinoma, (▲) adenocarcinoma.

TABLE VII
Excess Relative Risk per WLM[a] by Histological Cell Type and Its Variation with Several Factors

	(ERR/WLM) % by histological type		
	Squamous cell carcinoma (279)	Small cell carcinoma (69)	Adeno-carcinoma (46)
Overall	0.20	0.54	0.68
95% CI	(0.04–0.63)	(0.07–6.07)	(0.04–17.9)
Attained age			
<63	0.33	0.54	0.96
≥63	0.09	0.57	0.34
P^b	0.09	0.96	0.37
Years since last radon exposure			
<10	0.21	0.56	0.57
≥10	0.15	0.10	0.29
P^b	0.50	0.02	0.33
Radon progeny exposure rate (WLM/year)			
<25	0.52	0.82	0.59
≥25	0.23	0.57	0.69
P^b	0.01	0.45	0.79
Smoking status			
Never-smoker	—[c]	—[c]	1.96
Smoker	0.19	0.51	0.53
P^b	0.63	0.27	0.38
Years since cessation of smoking			
<5	0.20	0.31	0.43
≥5	0.25	—[c]	—[c]
P^b	0.85	0.41	0.58

Note. Numbers of cases given in parentheses.
[a] All models were stratified by smoking status, age, source of subject (Gejiu City or YTC) and type of respondent (individual or surrogate).
[b] *P* value for test of homogeneity of ERR/WLM over categories of modifying variables.
[c] Less than three lung cancer cases and ERR/WLM cannot be estimated.

cell carcinomas and relative to adenocarcinomas were 0.07 and 0.06, respectively; however, the sign of the test statistic indicated decreasing trends in the ORs with increasing WLM. This is due entirely to the notable difference between those exposed and those not exposed. Within each cell type, there is a relatively high percentage of nonexposed, 15% for squamous cell carcinomas, 19% for small cell carcinomas and 20% for adenocarcinomas, compared to the lowest WLM exposure category, which were 13, 9 and 7%, respectively. As a consequence, using the 1–199 WLM category as the referent level, the category-specific $OR_{SQ\text{-}SM}$ and $OR_{SQ\text{-}AD}$ estimates decline with increasing WLM, from 2.3 to 0.9 for small cell carcinomas and 3.8 to 0.6 for adenocarcinomas relative to squamous cell carcinomas, indicating that the proportion of squamous cell carcinomas compared to the referent tumor type decreases with exposure category. The patterns suggest that WLM exposure is more strongly associated with small cell carcinomas and adenocarcinomas. Table VIII shows that the declining patterns for the ORs occur principally in the subgroup of cases below the median age of 63. For ages 63 years and more, the $OR_{SQ\text{-}SM}$ estimates are flat, while the $OR_{SQ\text{-}AD}$ estimates are inconsistent. The *P* values for the test of homogeneity of the $OR_{SQ\text{-}SM}$ and the $OR_{SQ\text{-}AD}$ over the two age categories were 0.06 and 0.69, respectively, indicating that the differences in $OR_{SQ\text{-}AD}$ by age category may have arisen by chance. The patterns of decreasing ORs were also observed among cases who were current smokers or recent quitters. There were too few cases who were never-smokers or long-term ex-smokers to analyze.

DISCUSSION

The current study included detailed data on tobacco use patterns and WLM exposure for 460 incident lung cancer cases. The overall estimate of ERR/WLM was 0.28% with 95% CI of 0.1–0.6%, which was consistent with the 0.16% estimated from a related cohort mortality study of YTC workers *(6)*, which included 980 lung cancer deaths from 1976–1987 and which based WLM estimates on work history data from a 1976 occupational health survey. The patterns of variation in the ERR/WLM were also consistent with the YTC cohort study, as well as a joint analysis of 11 miner cohorts *(1)*. The ERR/WLM decreased with increasing attained age, time since last exposure to radon progeny and increasing exposure rate, while the ERR/WLM was not dependent on age at first exposure to radon progeny.

Consistent with several other studies of radon exposure and tobacco use, the ERR/WLM was higher in never-smokers than in smokers, but the difference was not statistically significant. This study showed for the first time that among smokers the estimate of radon-related lung cancer risk (ERR/WLM) was not affected by cessation of tobacco use or cessation of exposure to radon progeny. However, since there were only 9 cases who never smoked and 34 cases who were long-term ex-smokers, the power to estimate variations was limited. It should be noted that since the effects of exposure to radon progeny are approximately proportional to the background rate of lung cancer, and since stopping smoking reduces the risk of lung cancer, the absolute excess number of radon-induced lung cancer deaths would likely decline with smoking cessation.

Overall, our results support prior analyses of tobacco use and exposure to radon progeny, showing that the joint association is consistent with an association which is greater than additive *(1–3)*. We found no indication that the joint association of exposure to radon progeny and smoking was affected by attained age, rate of exposure to radon progeny, years since last radon exposure or cessation of smoking. These results may seem at odds with a recent study of cellular toxicity suggesting an additive effect of the "oncogenic transformation potential" for the joint association of exposure to

TABLE VIII
Numbers of Lung Cancer Cases and Odds Ratios[a] (OR) by Histological Type, Overall and within Categories of Attained Age and for Current smokers and Recent Ex-smokers

Histological type	Exposure to radon progeny (WLM) 0	1–199	200–399	400–799	≥800	Total
			All cases			
Squamous cell carcinoma	42 (15.1)	35 (12.5)	48 (17.2)	98 (35.1)	56 (20.1)	279
Small cell carcinoma	13 (18.8)	6 (8.7)	7 (10.1)	28 (40.6)	15 (21.7)	69
$OR_{SQ\cdot SM}$	1.00	2.25	2.20	0.99	0.91	
Adenocarcinoma	9 (19.6)	3 (6.5)	7 (15.2)	10 (21.7)	17 (37.0)	46
$OR_{SQ\cdot AD}$	1.00	3.75	1.35	1.63	0.56	
			Ages: < 63 years			
Squamous cell carcinoma	18 (13.2)	23 (16.9)	29 (21.3)	45 (33.1)	21 (15.4)	136
Small cell carcinoma	10 (30.3)	2 (6.1)	1 (3.0)	13 (39.4)	7 (21.2)	33
$OR_{SQ\cdot SM}$	1.00	6.03	12.3	1.50	1.01	
Adenocarcinoma	6 (20.7)	2 (6.9)	5 (17.2)	7 (24.1)	9 (31.0)	29
$OR_{SQ\cdot AD}$	1.00	5.24	1.60	1.34	0.61	
			Ages: ≥ 63 years			
Squamous cell carcinoma	24 (16.8)	12 (8.4)	19 (13.3)	53 (37.1)	35 (24.5)	143
Small cell carcinoma	3 (8.3)	4 (11.1)	6 (16.7)	15 (41.7)	8 (22.2)	36
$OR_{SQ\cdot SM}$	1.00	0.43	0.48	0.38	0.49	
Adenocarcinoma	3 (17.7)	1 (5.9)	2 (11.8)	3 (17.7)	8 (47.1)	17
$OR_{SQ\cdot AD}$	1.00	1.52	1.02	1.88	0.49	
			Current smokers or time since cessation of smoking < 5 years[b]			
Squamous cell carcinoma	39 (15.4)	32 (12.7)	46 (18.2)	91 (36.0)	45 (17.8)	253
Small cell carcinoma	13 (20.0)	5 (7.7)	7 (10.8)	25 (38.5)	15 (23.1)	65
$OR_{SQ\cdot SM}$	1.00	2.06	2.02	0.98	0.75	
Adenocarcinoma	8 (20.0)	3 (7.5)	7 (17.5)	9 (22.5)	13 (32.5)	40
$OR_{SQ\cdot AD}$	1.00	2.40	1.18	1.36	0.52	

Note. Percentages within cell type by WLM categories are given in parentheses.

[a] $OR_{SQ\text{-}SM}$ denotes odds ratio of squamous cell carcinomas to small cell carcinomas for a given exposure level relative to the referent level, and similarly, $OR_{SQ\text{-}AD}$ denotes odds ratio of squamous cell carcinomas to adenocarcinomas. Referent category is no WLM exposure.

[b] Never-smokers and long-term ex-smokers are not shown. There were 6 cases among never-smokers, 1 squamous carcinoma, 1 small carcinoma and 4 adenocarcinomas with mean WLM 182, 553 and 586, respectively. There were 30 cases among long-term ex-smokers, 25 squamous carcinomas, 3 small cell carcinomas and 2 adenocarcinomas, with mean WLM 692, 345 and 1,218, respectively.

radon progeny and tobacco smoke *(15).* However, the interpretation of results from such cellular-based studies in the context of lung cancer incidence in human populations is problematic, and a direct relationship may not hold.

Although the ERR/WLM was (nonsignificantly) larger in never-smokers than in smokers, the ERR/WLM estimates were less in the lower smoking rate groups than in the higher smoking rate groups (Table V). This pattern was also observed with smoking duration; the ERR/WLM was smallest in the lowest tertile of smoking duration (not shown). This may be somewhat surprising, as one may have expected that light smokers or short-duration smokers should exhibit risk patterns for radon exposure more similar to never-smokers. Seemingly, while the joint association between exposure to radon progeny and smoking status (smoker vs never-smoker) suggests a relationship between multiplicative and additive, among smokers the association between radon exposure and smoking rate (or duration) indicates a relationship greater than multiplicative. While these patterns may be due to chance, to the misspecification of smoking data or to unmeasured risk factors, there may also be fundamental differences in susceptibility to radon exposure between smokers and never-smokers. Many mechanisms by which radon progeny and smoking may interact are possible. It is known, for example, that smoking causes thickening of the bronchial mucosa, which may protect from the effects of the α particles, thereby potentially reducing the effects of radon exposure in smokers, while also reducing the rate of ciliary clearance, which may increase the chance of stem cell damage *(16).* The relative balance of these contrasting effects may be different by smoking status than in light compared to heavy smokers. These risk patterns, however, may also be affected by altered patterns of particle deposition consequent to smoking status and smoking rate *(16).*

We were able to assess the impact of the relative timing of exposure to radon progeny and tobacco use, finding a greater lung cancer risk when WLM and tobacco use occurred simultaneously than when tobacco use occurred entirely after cessation of radon exposure. This suggests that the effects of the two exposures are complementary for the carcinogenic process, either by acting at the same step of the carcinogenic process or by one exposure promoting the initiation activity of the other. Within this study, there were insufficient data to draw firm conclusions; it is known that tobacco smoking can act as a powerful promoter as well as an initiator. In analyses of the Colorado Plateau uranium miners *(17)* and of rats exposed to radon *(18)*, it has been suggested that both exposure to radon progeny and smoking affect the same steps in the carcinogenic process, namely, the first mutation rate of stem cells and the proliferation of intermediate cells. Experimental studies in animals of the role of smoking and exposure to radon progeny have been equivocal. Chameaud *et al.* *(19)* found an increase in tumor production when exposure to tobacco smoke followed exposure to radon progeny, while risk was not increased when exposure to tobacco smoke preceded exposure to radon. In contrast, Cross *et al.* *(20)* found that Wistar rats exposed to tobacco smoke after radon progeny had a longer mean survival time compared to rats exposed first to smoke, then to radon progeny. Uncertainties as to the effects of the temporal sequencing of tobacco smoking and exposure to radon progeny remain.

Early reports of the Colorado uranium miners suggested that radon exposure was more closely associated with small cell carcinomas, and that this pattern seemed to diminish as the cohort aged *(21)*. This observation was sustained in a comparative histology study of lung cancer cases among Colorado miners and Japanese atomic bomb survivors, where high-dose and low-dose cases underwent a uniform pathology review by a panel of experts *(22)*. Our analysis supports these conclusions. Although squamous cell carcinoma was the predominant tumor type, small cell carcinomas appeared more strongly associated with increased WLM exposure. Moreover, this association occurred primarily among miners who developed lung cancer at younger ages. In the Colorado data studied by Land *et al.*, there was no association between adenocarcinoma and WLM exposure; however, there were only eight cases. In our data, the adenocarcinomas also appeared more strongly associated with WLM exposure than were squamous cell carcinomas, although the differences in cell type were not statistically significant.

Adjustment for exposure to inorganic arsenic, a known lung carcinogen, reduced the estimates of RR (Table 1) and the estimate of the ERR/WLM, from 0.86% to 0.28%. Some may question whether the reduction in the ERR/WLM was the result of a high correlation between cumulative arsenic exposure and WLM. This appears unlikely to be a major factor, since among exposed miners, cumulative arsenic exposure and WLM had a correlation coefficient of 0.44, so that only about 20% of the variation in WLM exposure can be explained through arsenic exposure. In addition, the ERR/WLM estimates were homogeneous across arsenic exposure categories, defined by no exposure to arsenic and quartiles of cumulative arsenic exposure.

The results of this analysis should be interpreted cautiously, since information on 58% of cases and 13% of controls was obtained from next-of-kin interviews, which may have affected the quality of information, particularly regarding tobacco use. However, methodological studies have suggested that the quality of information from surrogate interviews is generally high if the information requested is not too detailed *(23, 24)*. Thus characterization of smoking status is likely quite accurate, but amount smoked may be less so. However, results were presented with adjustment for type of respondent. Further, results were generally unaffected when variables were assessed using only self-respondents.

Several new patterns of risk were identified in these data: (1) the ERR/WLM was similar in current smokers and recent quitters; (2) the association between exposure to radon progeny and tobacco use was likely intermediate between multiplicative and additive, and this relationship was unaffected by age, cessation of exposure to radon progeny, smoking status or years since cessation of smoking; (3) risk of lung cancer was higher if exposure to radon progeny and tobacco smoking overlapped in time compared to a temporal sequence in which smoking started only after radon exposure ceased; and (4) at younger ages, adenocarcinomas and small cell carcinomas appear to be more strongly associated with exposure to radon progeny than squamous cell carcinomas. While some of these patterns may have been due to chance, evaluations in other data sets should be carried out.

Received: November 12, 1993; accepted: January 4, 1994

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